REMARKS

Claims 1-44 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. As required by the Examiner, the replacement drawing sheets describe the different bars in the graphs of Figs. 6 and 8-9. Claims 5 and 10 were objected to as allegedly informal. Claim 5 is amended to define the term "ori" and claim 10 is amended to refer to a non-specific DNA binding protein.

Copies of Form PTO-1449 were returned, but it appears that the entries for "GB Search Report for related Appln. No. 0220759.5 dated 23 February 2003" and "Zubay 'In vitro synthesis of protein in microbial systems' Ann. Rev. Genet. 7:267-287 (1993)" were inadvertently not initialed by the Examiner. Applicants request that she extend the lines on Form PTO-1449 to confirm that the two documents are made of record, and return corrected copies of Form PTO-1449 to the undersigned.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-2, 4, 6, 10, 20-24, 27-32 and 34-44 were rejected under Section 102(b) as allegedly anticipated by Schatz *et al.* (U.S. Patent 6,156,511). Applicants traverse.

Claim 1 is directed to a method for producing a peptide expression library. Each peptide in this library is non-covalently linked to a DNA construct encoding the peptide. The method as claimed relies on the DNA construct and the protein that it encodes having cis-activity. That is, the encoded protein binds specifically to the DNA molecule from which it is being expressed. This permits specific binding of proteins only to their encoding DNA molecule. Because of this cis-activity, even if multiple different DNA constructs are expressed at the same time, each encoded protein will only bind to the specific DNA construct from which it is being produced. Thus, methods of the claimed

invention allow a variety of peptides to be simultaneously non-covalently attached to the DNA constructs that encode them. This advantage is reflected in claim 1 step (b) which requires a plurality of such DNA constructs to be expressed, thereby producing a library of peptide-DNA construct molecules.

The Schatz *et al.* document does not teach how such a library can be produced. In particular, Schatz *et al.* do not teach how more than one of such molecules could be produced at the same time, without the risk that the expressed peptides would bind to other DNA constructs in the mixture, rather than just the specific DNA construct that encoded them.

As noted by the Examiner, Schatz *et al.* teach that the DNA binding protein can bind to the recombinant DNA expression vector encoding it. Schatz *et al.* suggest that a suitable system may make use of the lac repressor operon, which DNA binds the lac repressor protein. This will indeed allow for a given peptide, when fused to the lac repressor protein, to bind specifically to the lac repressor operon. Such a system, however, does not have cis activity as required by claim 1. As explained above, cis-activity requires the expressed protein to bind specifically to the DNA molecule from which it was expressed, not just to any DNA molecule having a particular binding site. The methods described in Schatz *et al.* do not, therefore, meet the requirements of claim 1.

To illustrate this difference, we can look again at claim 1 step (b), which requires that a plurality of DNA constructs are expressed together such that each expressed peptide is non-covalently linked to the DNA from which it was produced. If more than one DNA construct as described in Schatz *et al.* was expressed at the same time, specific binding only to the encoding DNA construct would not occur. Any "lac repressor protein" in such a mixture could bind any "lac repressor DNA binding site" in the mixture. The lack of cis-activity in this system means that the encoded peptides would be just as likely to bind to a different DNA construct as to the DNA construct from which they have been expressed. It would therefore not be possible to carry out a method according to claim 1 using the DNA constructs as described in Schatz *et al.*

The Examiner has referred to various passages in Schatz *et al.* (column 5, lines 1-11; column 9, lines 32-48; column 16, lines 49-67). These passages refer to the possible presence of a spacer region within the described peptides. Schatz *et al.* teach that such spacers may be used to alter the overall configuration of the protein: for example, to minimize the steric hindrance to the peptide of interest from the presence of the DNA binding protein in the same polypeptide chain. The presence of such a spacer may well improve the ability of the DNA binding protein to bind to DNA. But this does not mean that the DNA and encoded protein have cis-activity. The presence of cis-activity as required by Applicants' claimed invention means that the encoded protein will bind specifically to the DNA molecule encoding it, not to any other DNA molecules, even if they are identical in nucleotide sequence to the encoding sequence. This feature is neither taught nor suggested by Schatz *et al.* Using the method of Schatz *et al.*, it would be necessary to express each peptide separately, for example in a different cell, and allow it to bind to its DNA construct before that peptide-DNA molecule is combined with any other similar molecules. This would be the only way to ensure that each peptide binds the correct DNA molecule. The molecules described by Schatz *et al.* are therefore not suitable for use in the method of claim 1. Schatz *et al.* do not have the required cis-activity and it would not be possible to carry out claim 1 step (b) using such molecules.

There is no teaching in Schatz *et al.* that would lead one to Applicants' claimed invention. There is also no suggestion in Schatz *et al.* that a cis-acting protein and DNA sequence might be utilized in this way. Applicants' claimed invention is therefore not anticipated by Schatz *et al.*

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a

person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn*, 78 USPQ2d at 1335; see *KSR*, 82 USPQ2d at 1396. A claim which is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 1396. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 3, 5 and 7-9 were rejected under Section 103(a) as allegedly unpatentable over Schatz *et al.* (U.S. Patent 6,156,511) in view of Praszkier *et al.* (J. Bacteriol. 181:2765-2772, 1999). Applicants traverse.

The disclosure of Schatz *et al.* and its failure to teach the invention of claim 1 is discussed above. The Examiner's obviousness rejections are all based on the Schatz *et al.* document. As explained above, however, the Schatz *et al.* document fails to disclose a method according to claim 1 wherein the DNA construct and encoded protein are selected to have cis-activity. Schatz *et al.* do not teach or suggest a method wherein a plurality of different DNA constructs are expressed together and each expressed peptide is non-covalently linked to the DNA from which it was produced. It would not be possible to carry out such a method using the molecules described by Schatz *et al.*

As noted by the Examiner, Schatz *et al.* do not teach that the repA and ori sequences could be utilized in such a method. In fact, Schatz *et al.* do not teach that any cis-acting molecules could be utilized in this way. The Examiner cited Praszkier *et al.* and suggested that one of ordinary skill in the art would have combined the Praszkier *et al.* and Schatz *et al.* disclosures. Applicants submit that the Examiner's reasoning here is based on hindsight and knowledge of the present invention. Praszkier *et al.* discuss the repA/ori system, but does not suggest any particular use of this system. In contrast, Schatz *et al.* discuss a variety of different peptides and DNA binding proteins that could be used in the described methods, but does not at any point suggest that a cis-acting protein might be of particular use. One of ordinary skill in the art reading Schatz *et al.* would have had no reason to combine it with Praszkier *et al.* Given the large number of different DNA binding proteins that are disclosed in Schatz *et al.*, one of ordinary skill in the art would have had no reason or motivation to use a different DNA binding protein that is not even mentioned by Schatz *et al.*

In fact, Applicants' claimed invention provides advantages that are unexpected because they are neither suggested nor envisaged by the prior art of record. By using a cis-acting protein rather than any other DNA binding protein, Applicants' invention may be practiced. In particular, it is possible to express a plurality of different DNA constructs at the same time with the knowledge and understanding that each expressed peptide will bind only to the DNA molecule encoding it. This allows a much simpler and easier method for preparing a library of expressed peptides, wherein each peptide is linked to its encoding DNA sequence. There is nothing in Schatz *et al.* which suggests that such an improvement might be achievable. There is nothing in Praszkier *et al.* that suggests that the repA/ori system might be applicable to such a method. One of ordinary skill in the art at the priority date would have had no reason to combine these two documents and would not have anticipated the unexpected advantages that could be achieved by utilizing a cis-acting molecule in such a method.

For the reasons discussed above, Applicants' claimed invention is submitted not to be obvious over Schatz *et al.* in view of Praszkier *et al.* or the other documents cited by the Examiner (see below).

Claim 33 was rejected under Section 103(a) as allegedly unpatentable over Schatz *et al.* in view of Edwards *et al.* (U.S. Patent 5,716,780). Applicants traverse.

The disclosure of Schatz *et al.* and its failure to anticipate the invention of claim 1 are discussed above. This failure is not remedied by citation of the Edwards *et al.* document. Therefore, the combination of Schatz *et al.* and Edwards *et al.* does not render obvious the subject matter of claim 33.

Claim 25 was rejected under Section 103(a) as allegedly unpatentable over Schatz *et al.* and Szostak *et al.* (U.S. Patent 6,281,344) in view of Mattheakis *et al.* (Proc. Natl. Acad. Sci. USA 91:9022-9026, 1994). Applicants traverse.

The disclosure of Schatz *et al.* and its failure to anticipate the invention of claim 1 are discussed above. This failure is not remedied by citation of the Szostak *et al.* and Mattheakis *et al.* documents. Therefore, the combination of Schatz *et al.*, Szostak *et al.*, and Mattheakis *et al.* does not render obvious the subject matter of claim 25.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art at the time Applicants made their invention.

Conclusion

Having fully responded to all objections and rejection contained in this Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /Gary R. Tanigawa/
Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100